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(21) International Application Number: PCT/SE98/02028 (22) International Filing Date: 10 November 1998 (10.11.98) (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): LÖVQVIST, Karin [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). NORELAND, David [SE/SE]; Astra Production Chemicals AB, S-151 85 Södertälje (SE). SUNDÉN, Gunnar [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). YMÉN, Ingvar [SE/SE]; Astra Production Chemicals AB, S-151 85 Södertälje (SE). (74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Upon the request of the applicant, before the expiration of the time limit referred to in Article 21(2)(a). Without international search report and to be republished upon receipt of that report. Without classification; title and abstract not checked by the International Searching Authority.</i>	
(54) Title: NEW CRYSTALLINE FORM OF OMEPRAZOLE (57) Abstract The present invention relates to a novel crystalline form of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl- 2-pyridinyl)methyl] sulfinyl]-1H- benzimidazole, known under the generic name omeprazole. Further, the present invention also relates to the use of the novel crystalline form of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl- 2-pyridinyl)methyl] sulfinyl]-1H- benzimidazole for the treatment of gastrointestinal disorders, pharmaceutical compositions containing it as well as processes for the preparation of the novel crystalline form of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl- 2-pyridinyl)methyl] sulfinyl]-1H- benzimidazole.			

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NEW CRYSTALLINE FORM OF OMEPRAZOLE

Field of the invention

5 The present invention relates to a novel crystalline form of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole. 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole is known under the generic name omeprazole and its novel crystalline form is hereinafter referred to as omeprazole form A. Further, the present invention also relates to use of omeprazole form A for the treatment of

10 gastrointestinal disorders, pharmaceutical compositions containing omeprazole form A and processes for the preparation of omeprazole form A.

Background of the invention and prior art

15 The compound 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, as well as therapeutically acceptable salts thereof, are described in EP 5129. The single crystal X-ray data and the derived molecular structure of the so far only known crystal form of omeprazole is described by Ohishi *et al.*, *Acta Cryst.* (1989), C45, 1921-1923. This published crystal form of

20 omeprazole is hereinafter referred to as omeprazole form B.

Omeprazole is a proton pump inhibitor, *i.e.* effective in inhibiting gastric acid secretion, and is useful as an antiulcer agent. In a more general sense, omeprazole may be used for treatment of gastric-acid related diseases in mammals and especially in man.

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Brief description of the drawings

Figure 1 is an X-ray powder diffractogram of omeprazole form A.

Figure 2 is an X-ray powder diffractogram of omeprazole form B.

Description of the invention

It has surprisingly been found that the substance omeprazole can exist in more than one crystal form. It is an object of the present invention to provide omeprazole form A. Another object of the present invention is to provide a process for the preparation of omeprazole form A, substantially free from other forms of omeprazole. X-ray powder diffraction (XRPD) is used as a method of differentiating omeprazole form A from other crystalline and non-crystalline forms of omeprazole. Additionally it is an object of the present invention to provide pharmaceutical formulations comprising omeprazole form A.

Omeprazole form A is a crystalline form exhibiting advantageous properties, such as being well-defined, being thermodynamically more stable and less hygroscopic than omeprazole form B, especially at room temperature. Omeprazole form A does also show a better chemical stability, such as thermo stability and light stability, than omeprazole form B.

Omeprazole form B can under certain conditions, completely or partly, be converted into omeprazole form A. Omeprazole form A is thereby characterized in being thermodynamically more stable than omeprazole form B.

Omeprazole form A is further characterized as being essentially non-hygroscopic.

Omeprazole form A is characterized by the positions and intensities of the peaks in the X-ray powder diffractogram, as well as by the unit cell parameters. The unit cell dimensions have been calculated from accurate Guinier data. The X-ray powder diffractogram data as well as the unit cell parameters for omeprazole form B are different compared to omeprazole form A. Omeprazole form A can thereby be distinguished from omeprazole form B, using X-ray powder diffraction.

Omeprazole form A, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 1, exhibiting substantially the following d-values and intensities;

Form A		Form A	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
9.5	vs	3.71	s
7.9	s	3.59	m
7.4	w	3.48	m
7.2	vs	3.45	s
6.0	m	3.31	w
5.6	s	3.22	s
5.2	s	3.17	m
5.1	s	3.11	w
4.89	w	3.04	w
4.64	m	3.00	w
4.60	m	2.91	w
4.53	w	2.86	w
4.49	m	2.85	w
4.31	m	2.75	w
4.19	w	2.67	w
4.15	w	2.45	w
3.95	w	2.41	w

The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the Guinier diffractogram of omeprazole form A. The relative

intensities are less reliable and instead of numerical values the following definitions are used;

	% Relative Intensity*	Definition
5	25-100	vs (very strong)
	10-25	s (strong)
	3-10	m (medium)
	1-3	w (weak)

* The relative intensities are derived from diffractograms measured with fixed slits.

10

Omeprazole form A according to the present invention is further characterized by a triclinic unit cell with parameters;

$$a=10.410(4) \text{ \AA}$$

$$b=10.468(3) \text{ \AA}$$

$$c=9.729(4) \text{ \AA}$$

$$\alpha=111.51(3)^\circ$$

$$\beta=116.78(3)^\circ$$

$$\gamma=90.77(3)^\circ$$

15 Omeprazole form A can also be characterized by Raman spectroscopy, where omeprazole form A is characterized by the absence of a band at 1364 cm^{-1} , which is observed for omeprazole form B, and by the ratio of the relative intensities of the 842 and 836 cm^{-1} bands. The ratio (intensity of 842 cm^{-1} band / intensity of 836 cm^{-1} band) is <1 for omeprazole form A, while the ratio is >1 for omeprazole form B.

20

According to the invention there is further provided a process for the preparation of omeprazole form A.

Omeprazole form A is obtained upon slow crystallization and omeprazole form B is obtained from fast crystallization. Omeprazole form A may be prepared by reaction crystallisation or recrystallizing omeprazole of any form, or mixtures of any forms, in an appropriate solvent, such as for instance methanol, at around room temperature and for a prolonged time period. Examples of prolonged time periods include, but are not limited to, a few hours, such as 2 hours, up to several weeks. Suitable solvents are alkyl alcohols and especially a lower alcohol comprising 1 - 4 carbon atoms.

Omeprazole form A may also be prepared by suspending omeprazole of any form, or mixtures of any forms, in an appropriate solvent at around room temperature and for a prolonged time period. Examples of appropriate solvents include, but are not limited to, methanol, ethanol, acetone, ethyl acetate, methyl tert. butyl ether, toluene, or any mixture thereof. Examples of prolonged time periods include, but are not limited to, a few hours, such as 2 hours, up to several weeks.

The omeprazole form A obtained according to the present invention is substantially free from other crystal and non-crystal forms of omeprazole, such as omeprazole form B. Substantially free from other forms of omeprazole shall be understood to mean that omeprazole form A contains less than 10%, preferably less than 5%, of any other forms of omeprazole, *e.g.* omeprazole form B.

Omeprazole form A in mixture with other solid form/forms of omeprazole, *e.g.* omeprazole form B, also exhibits advantageous properties, such as being chemically more stable than pure omeprazole form B. Mixtures comprising a certain amount of omeprazole form A, by weight, are also chemically more stable than other mixtures comprising a lesser amount of omeprazole form A, by weight. Such mixtures comprising omeprazole form A can be prepared, for example, by mixing omeprazole form A prepared according to the present invention with other solid forms of omeprazole, such as form B, prepared according to prior art.

The present invention also relates to mixtures comprising omeprazole form A in mixture with other solid forms of omeprazole. Such mixtures comprising omeprazole form A include for instance mixtures containing a detectable amount of omeprazole form A, 1%, 2%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 98% or 99% (by weight), of omeprazole form A.

Examples of other solid forms of omeprazole include, but are not limited to, omeprazole form B, amorphous forms, and other polymorphs.

10 A detectable amount of omeprazole form A is an amount that can be detected using conventional techniques, such as FT-IR, Raman spectroscopy, XRPD and the like.

The expression chemical stability includes, but is not limited to, thermo stability and light stability.

15 The compound of the invention, *i.e.* omeprazole form A, prepared according to the present invention is analyzed, characterized and differentiated from omeprazole form B by X-ray powder diffraction, a technique which is known per se. Another suitable technique to analyze, characterize and differentiate omeprazole form A from omeprazole form B is by Raman spectroscopy.

20 Omeprazole form A is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, it can be used for treatment of gastric-acid related conditions in mammals and especially in man, including *e.g.* reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable *e.g.* in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. The compound of the invention may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent

aspiration of gastric acid and to treat stress ulceration. Further, the compound of the invention may be useful in the treatment of psoriasis as well as in the treatment of *Helicobacter* infections and diseases related to these. The compound of the invention may also be used for treatment of inflammatory conditions in mammals, including man.

5

Any suitable route of administration may be employed for providing the patient with an effective dosage of omeprazole form A according to the invention. For example, peroral or parenteral formulations and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions and the like, *e.g.* enteric-coated capsules and/or tablets, 10 capsules and/or tablets containing enteric-coated pellets of omeprazole. In all dosage forms omeprazole form A can be admixed with other suitable constituents. .

According to the invention there is further provided a pharmaceutical composition comprising omeprazole form A, as active ingredient, in association with a pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. 15 Compositions comprising other therapeutic ingredients are especially of interest in the treatment of *Helicobacter* infections. The invention also provides the use of omeprazole form A in the manufacture of a medicament for use in the treatment of a gastric-acid related condition and a method of treating a gastric-acid related condition which method 20 comprises administering to a subject suffering from said condition a therapeutically effective amount of omeprazole form A.

The compositions of the invention include compositions suitable for peroral or parenteral administration. The compositions may be conveniently presented in unit dosage forms, and 25 prepared by any methods known in the art of pharmacy.

In the practice of the invention, the most suitable route of administration as well as the magnitude of a therapeutic dose of omeprazole form A in any given case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also 30 vary according to the age, body weight, and response of the individual patient. Special

requirements may be needed for patients having Zollinger-Ellison syndrome, such as a need for higher doses than the average patient. Children and patients with liver diseases as well as patients under long term treatment will generally benefit from doses that are somewhat lower than the average. Thus, in some conditions it may be necessary to use 5 doses outside the ranges stated below. Such higher and lower doses are within the scope of the present invention.

In general, a suitable oral dosage form may cover a dose range from 5 mg to 250 mg total daily dose, administered in one single dose or equally divided doses. A preferred dosage 10 range is from 10 mg to 80 mg.

The compound of the invention may be combined as the active component in intimate admixture with a pharmaceutical carrier according to conventional techniques, such as the oral formulations described in WO 96/01623 and EP 247 983, the disclosures of which are 15 hereby incorporated as a whole by reference.

Combination therapies comprising omeprazole form A and other active ingredients in separate dosage forms, or in one fixed dosage form, may also be used. Examples of such active ingredients include anti-bacterial compounds, non-steroidal anti-inflammatory 20 agents, antacid agents, alginates and prokinetic agents.

The examples which follow will further illustrate the preparation of the compound of the invention, i.e. omeprazole form A, but are not intended to limit the scope of the invention as defined hereinabove or as claimed below.

25

Examples

Example 1

Preparation of omeprazole form A

Omeprazole (55.8 g) is added at room temperature to methanol (348 ml) containing ammonia (1.3 ml; 25%). The suspension is thereafter stirred in darkness for approximately 5 45 hours and then filtered. The filtrate is dried 18 hours at 30°C under reduced pressure (<5 mbar). Yield: 43.9 g.

Example 2

10 *Preparation of omeprazole form B*

Omeprazole (50 g) is added to methanol (750 ml) containing ammonia (0.7 ml; 25%) at 50°C. The solution is thereafter filtered and cooled in about 20 minutes to approximately 0°C. The formed crystals are filtered and washed with ice cooled methanol and then dried. 15 The filtrate was dried 24 hours at 40°C under reduced pressure (<5 mbar). Yield: 39 g.

Example 3

20 *Characterization of omeprazole form A and omeprazole form B using X-ray powder diffraction*

X-ray diffraction analysis was performed according to standard methods which can be found in e.g. Bunn, C. W. (1948), Chemical Crystallography, Clarendon Press, London; or Klug, H.P. & Alexander, L. E. (1974), X-Ray Diffraction Procedures, John Wiley and Sons, New York. The unit cell parameters for omeprazole form A and B have been 25 calculated from the Guinier X-ray powder diffractograms using the program "TREOR" by Werner, P.-E., Eriksson, L. and Westdahl, M., J. Appl. Crystallogr. 18 (1985) 367 - 370. The fact that the positions of all peaks in the diffractograms for omeprazole form A and form B may be calculated using the respective unit cell parameters, proves that the unit cells are

correct and that the diffractograms are indicative of the pure forms. The diffractogram of omeprazole form A, prepared according to Example 1 in the present application, is shown in Figure 1 and the diffractogram of omeprazole form B, prepared according to Example 2 in the present application is shown in Figure 2.

5

The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the diffractograms for omeprazole forms A and form B, and are given in Table 1. In this table the unit cell parameters for omeprazole forms A and B are also given. The relative intensities are less reliable and instead of numerical values the 10 following definitions are used;

% Relative Intensity	Definition
25-100	vs (very strong)
10-25	s (strong)
15 3-10	m (medium)
1-3	w (weak)

Some additional weak or very weak peaks found in the diffractograms have been omitted from table 1.

20

Table 1. X-ray powder diffraction data for omeprazole form A and form B shown in Figures 1 and 2. All peaks noted for omeprazole form A and form B can be indexed with the unit cells given below.

Form A		Form B	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
9.5	vs	9.6	vs
7.9	s	8.0	m
7.4	w	7.9	m
7.2	vs	7.5	w
6.0	m	7.1	vs
5.6	s	5.9	m
5.2	s	5.6	m
5.1	s	5.3	s
4.89	w	5.1	s
4.64	m	4.54	m
4.60	m	4.48	s
4.53	w	4.41	m
4.49	m	4.14	w
4.31	m	3.75	s
4.19	w	3.57	m
4.15	w	3.47	s
3.95	w	3.40	w
3.71	s	3.28	s
3.59	m	3.22	m
3.48	m	3.02	w
3.45	s	2.97	w

Form A		Form B	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
3.31	w	2.87	w
3.22	s	2.37	w
3.17	m		
3.11	w		
3.04	w		
3.00	w		
2.91	w		
2.86	w		
2.85	w		
2.75	w		
2.67	w		
2.45	w		
2.41	w		

The triclinic unit cells are:

Unit cell form A

$a=10.410(4)$ Å

$b=10.468(3)$ Å

$c=9.729(4)$ Å

$\alpha=111.51(3)$ °

$\beta=116.78(3)$ °

$\gamma=90.77(3)$ °

Unit cell form B

$a=10.257(10)$ Å

$b=10.717(6)$ Å

$c=9.694(10)$ Å

$\alpha=112.14(7)$ °

$\beta=115.56(5)$ °

$\gamma=91.76 (7)$ °

CLAIMS

1. Omeprazole form A, characterized in being thermodynamically stable at room temperature.
- 5
2. Omeprazole form A, characterized in being essentially non-hygroscopic.
3. Omeprazole form A according to claims 1 or 2, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values;

10

Form A		Form A	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
9.5	vs	3.71	s
7.9	s	3.59	m
7.4	w	3.48	m
7.2	vs	3.45	s
6.0	m	3.31	w
5.6	s	3.22	s
5.2	s	3.17	m
5.1	s	3.11	w
4.89	w	3.04	w
4.64	m	3.00	w
4.60	m	2.91	w
4.53	w	2.86	w
4.49	m	2.85	w
4.31	m	2.75	w
4.19	w	2.67	w
4.15	w	2.45	w
3.95	w	2.41	w

4. Omeprazole form A, according to any of claims 1-3, characterized by having a triclinic unit cell with parameters

5 $a=10.410(4) \text{ \AA}$, $b=10.468(3) \text{ \AA}$, $c=9.729(4) \text{ \AA}$, $\alpha=111.51(3)^\circ$, $\beta=116.78(3)^\circ$,
 $\gamma=90.77(3)^\circ$.

10 5. Omeprazole, characterized in containing more than 50%, by weight, of omeprazole form A according to any of claims 1-4.

15 6. A process for the preparation of omeprazole form A as defined in any of claims 1-4, comprising the steps of;

15 a) dissolving or suspending omeprazole of any form, or a mixture of any form, in a suitable solvent;

15 b) allowing the solution to crystallize, optionally using omeprazole form A to induce crystallization, and

15 c) isolating the omeprazole form A thus obtained.

20 7. A process according to claim 6, characterized in that the solvent used in step a) is chosen from a group consisting of methanol, ethanol, acetone, ethyl acetate, methyl tert. butyl ether, toluene, or any mixture thereof.

25 8. A process according to claims 6 or 7, characterized in that step a) is performed at 15-25°C.

25 9. A process according to any of claims 6-8, characterized in that step b) is performed during a prolonged time period.

10. A process according to any claim 6-9, characterized in that step b) is performed during at least 2 hours.

11. Omeprazole form A, prepared by a process according to any of claims 6-10.

5

12. A pharmaceutical formulation comprising omeprazole as defined in any of claims 1-5 in admixture with a pharmaceutically acceptable excipient.

10 13. The use of omeprazole as defined in any of claims 1-5, as active ingredient in the manufacture of medicament for use in treatment of gastrointestinal disorders.

14. A method of treatment of gastrointestinal disorders which comprises administration of a therapeutically effective amount of omeprazole as defined in any of claims 1-5, to a patient suffering from gastrointestinal disorders.

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Fig. 1 An X-ray powder diffractogram of omeprazole form A measured with variable slits.

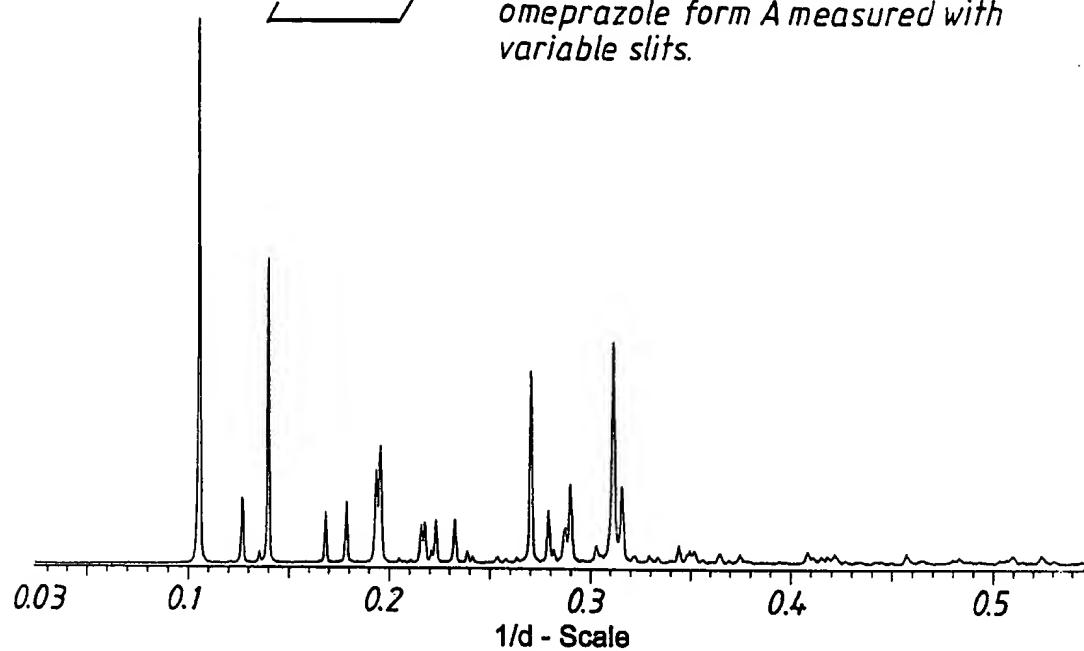
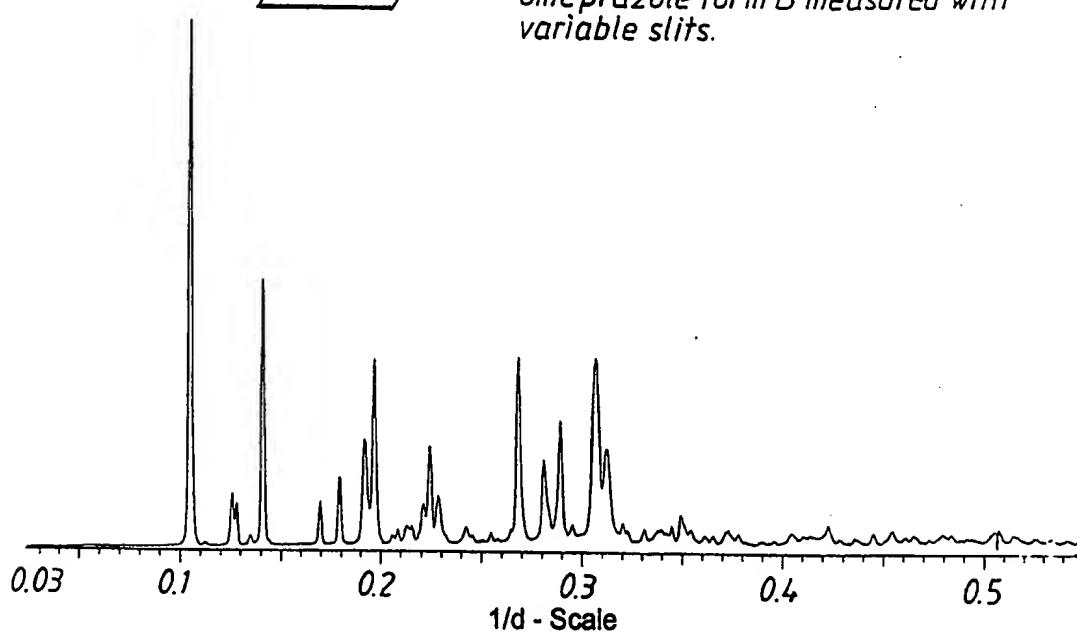


Fig. 2 An X-ray powder diffractogram of omeprazole form B measured with variable slits.



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(54) Title: **NEW CRYSTALLINE FORM OF OMEPRAZOLE**

(57) Abstract

The present invention relates to a novel crystalline form of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole, known under the generic name omeprazole. Further, the present invention also relates to the use of the novel crystalline form of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole for the treatment of gastrointestinal disorders, pharmaceutical compositions containing it as well as processes for the preparation of the novel crystalline form of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole.

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AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/02028

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 401/12, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Acta Cryst., Volume C45, 1989, Hirofumi Ohishi et al, "Structure of 5-Methoxy-2-((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole (Omeprazole)" page 1921 - page 1923 --	1-13
A	EP 0005129 A1 (AKTIEBOLAGET HÄSSLE), 31 October 1979 (31.10.79) -- -----	1-13

<input type="checkbox"/>	Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/> See patent family annex.
* Special categories of cited documents		
"A" document defining the general state of the art which is not considered to be of particular relevance	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier document but published on or after the international filing date	"X"	document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
<u>30 April 1999</u>	<u>10 -06- 1999</u>
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/02028

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 14 because they relate to subject matter not required to be searched by this Authority, namely:
A method for treatment of the human or animal body by therapy, see rule 39.1
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.



No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

07/04/99

International application No.	
PCT/SE 98/02028	

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT
Information on patent family members

07/04/99

International application No.
PCT/SE 98/02028

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